P&T®

PRODUCT PROFILER

WARNING: BLEEDING RISK

- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75 mg to 100 mg per day

This section of P&T was developed with input from and supported by AstraZeneca.

Please read Important Safety Information on page 2 and accompanying Full Prescribing Information, including Boxed Warnings and Medication Guide.

Brilinta™

(ticagrelor) Tablets

FDA-approved indication

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined end point of cardiovascular death, myocardial infarction, or stroke compared with clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

BRILINTA has been studied in ACS patients in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses above 100 mg daily.

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The Product Profiler

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

About the Authors

Carole Alison Chrvala, PhD, was trained as an epidemiologist at the University of Colorado. Dr. Chrvala is a seasoned researcher and medical writer with 22 years experience in chronic disease screening, diagnosis, treatment, and evaluation. Highlighting a career that spanned the public and private health sectors, Dr. Chrvala was director of Cancer Prevention and Control for the Colorado Department of Public Health and Environment (CDPHE). During her tenure at CDPHE, she was a principal investigator or co-principal investigator on more than 10 grants, contracts, and cooperative agreements. Dr. Chrvala also served as invited reviewer for several National Institutes of Health (NIH) grant review panels, and has had the honor of participating on a variety of advisory boards and steering committees on cancer, diabetes, cardiovascular disease, HIV/AIDS, and women's health.

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Dr. Caspi has served on the editorial advisory boards of The Pharmaceutical Biotechnology Monitor: Biotechnology Issues for the Pharmacist and Global Medical Communications. He currently serves on the editorial board of *P&T* and coordinates the journal's Drug Forecast department.

Disclosures

Carole Alison Chrvala, PhD, and Alan Caspi, PhD, PharmD, MBA, both report that they have no financial arrangements or affiliations that might constitute a conflict of interest with respect to this publication. AstraZeneca provided funding for this publication.

See page 19 for Full Prescribing Information

PRODUCT PROFILER

Brilinta™

(ticagrelor) Tablets

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See page 19 for Full Prescribing Information

Important Safety Information About BRILINTA™ (ticagrelor) Tablets

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- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures in the setting of BRILINTA
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75 mg to 100 mg per day

CONTRAINDICATIONS

- BRILINTA is contraindicated in patients with a history of intracranial hemorrhage and active pathological bleeding, such as peptic ulcer or intracranial hemorrhage. BRILINTA is also contraindicated in patients with severe hepatic impairment because of a probable increase in exposure; it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins

See page 19 for Full Prescribing Information

WARNINGS AND PRECAUTIONS

- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor
- Premature discontinuation increases the risk of MI, stent thrombosis, and death
- Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes
- BRILINTA is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors and potent CYP3A inducers. Avoid simvastatin and lovastatin above 40 mg
- Monitor digoxin levels with initiation of, or any change in, BRILINTA therapy

ADVERSE REACTIONS

- The most commonly observed adverse reactions associated with the use of BRILINTA vs. clopidogrel were total major bleeding (11.6% vs. 11.2%) and dyspnea (14% vs. 8%)
- In clinical studies, BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias. PLATO excluded patients at increased risk of bradycardic events. Consider the risks and benefits of treatment

Please read the Full Prescribing Information, including Boxed Warnings and Medication Guide.

See page 19 for Full Prescribing Information

BRILINTA™ (ticagrelor) Tablets

A $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS)

INTRODUCTION

This Product Profiler introduces health care professionals to BRILINTA (ticagrelor), a $P2Y_{12}$ platelet inhibitor that reversibly binds with the platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptor to prevent signal transduction and platelet activation (BRILINTA Prescribing Information 2011). Ticagrelor is not a prodrug and does not require metabolic activation to inhibit the $P2Y_{12}$ receptor; however, it is converted in the liver into an active metabolite, which is approximately equipotent (James 2009).

BRILINTA has been approved by the FDA to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS), including unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) (FDA 2011, BRILINTA Prescribing Information 2011). BRILINTA has been shown to reduce the rate of a combined end point of cardiovascular (CV) death, myocardial infarction (MI), or stroke compared with clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily.

In the pivotal phase-3 PLATelet inhibition and patient Outcomes (PLATO) trial, which compared BRILINTA (n = 9,333) with clopidogrel (n = 9,291) in patients with ACS, BRILINTA significantly reduced the rate of first occurrence of the study's composite end point of cardiovascular death, nonfatal MI (excluding silent MI), or stroke. BRILINTA also reduced the secondary end points of cardiovascular death and MI individually, with no difference in stroke (BRILINTA Prescribing Information 2011).

The following text presents an overview of the evidence supporting the FDA-approved indication for BRILINTA in patients with ACS, and considerations for P&T committee decisions regarding this product.

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- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events

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Please read additional Important Safety Information on page 2.

See page 19 for Full Prescribing Information

Product Information

CONTRAINDICATIONS

History of Intracranial Hemorrhage

BRILINTA™ is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population.

Active Bleeding

BRILINTA is contraindicated in patients with active pathological bleeding, such as peptic ulcer or intracranial hemorrhage.

Severe Hepatic Impairment

BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins.

DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, which inhibits platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor. The chemical structure of ticagrelor is shown in Figure 1.

Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 mcg/mL at room temperature.

BRILINTA tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ticagrelor and its major (active) metabolite (AR-C124910XX) interact with the platelet $P2Y_{12}$ ADP receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6-week study that examined both acute and chronic platelet inhibition effects in response to 20 mcM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study after loading doses of 180 mg ticagrelor or 600 mg clopidogrel. IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at approximately 2 hours and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 mcM ADP. The mean maximum IPA after the last dose of ticagrelor and clopidogrel was 88% and 62%, respectively. After 24 hours, IPA in the ticagrelor group (58%) was similar to that in the clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk correlate with IPA for either ticagrelor or clopidogrel.

Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4%, and transitioning from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interrupting the drug's antiplatelet effect.

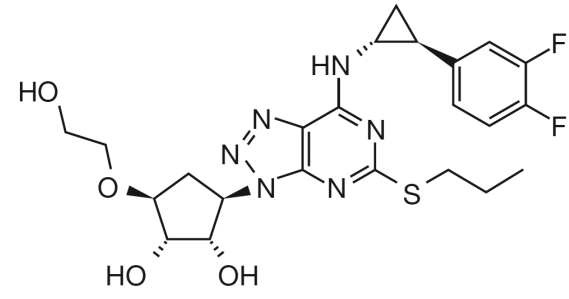
Pharmacokinetics

Ticagrelor demonstrates dose-proportional pharmacokinetic characteristics, which are similar in patients and healthy volunteers.

Absorption. Absorption of ticagrelor occurs with a median time to maximum plasma concentration (t_{max}) of 1.5 hours (range, 1.0 to 4.0 hours). The formation of the major (active) circulating metabolite AR-C124910XX from ticagrelor occurs with a median t_{max} of 2.5 hours (range, 1.5 to 5.0 hours).

The mean absolute bioavailability of ticagrelor is approximately 36% (range, 30% to 42%). Ingestion of a

FIGURE 1
Chemical Structure of Ticagrelor



Source: BRILINTA Prescribing Information 2011.

See page 19 for Full Prescribing Information

high-fat meal had no effect on the maximum plasma concentration (C_{max}) of ticagrelor, but resulted in a 21% increase in the area under the concentration–time curve (AUC). The C_{max} of the major metabolite of ticagrelor was decreased by 22%, with no change in AUC. BRILINTA™ can be taken with or without food.

Distribution. The steady-state volume of distribution of ticagrelor is 88 L. Ticagrelor and its active metabolite are extensively bound to human plasma proteins (> 99%).

Metabolism. CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30% to 40% of the exposure of ticagrelor.

Excretion. The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean half-life is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Special Populations. The effects of age, gender, ethnicity, renal impairment, and mild hepatic impairment on the pharmacokinetics of ticagrelor are modest and do not require dose adjustment. Ticagrelor has not been evaluated in a pediatric population. No dose adjustment is necessary for ticagrelor based on weight.

Habitual smoking increased the population mean clearance of ticagrelor by approximately 22% when compared with nonsmokers. No dose adjustment is necessary for ticagrelor based on smoking status.

BRILINTA has not been studied in patients with moderate to severe hepatic impairment. For patients with moderate hepatic impairment, consider the risks and benefits of treatment and carefully consider use. BRILINTA is contraindicated in patients with severe hepatic impairment.

BRILINTA was not studied in patients undergoing renal dialysis.

The key pharmacokinetic characteristics of BRILINTA are summarized in Table 1.

Effects of Other Drugs on BRILINTA

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Strong CYP3A inhibitors (eg, ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors (eg, diltiazem) have lesser effects. CYP3A inducers (eg, rifampin) substantially reduce ticagrelor blood levels.

Effects of BRILINTA on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5, and inhibitors of the P-glycoprotein transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C9, and CYP2E1 activity.

TABLE 1
Key Pharmacokinetic Characteristics of BRILINTA

Absorption	• Absorption of ticagrelor occurs with a median t_{max} of 1.5 hours (range: 1.0 to 4.0 hours). • The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 hours (range, 1.5 to 5.0 hours).
Distribution	• The steady-state volume of distribution of ticagrelor is 88 L. • Ticagrelor and the active metabolite are extensively bound to human plasma proteins (> 99%).
Metabolism	• CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. • Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. • The systemic exposure to the active metabolite is approximately 30% to 40% of the exposure of ticagrelor.
Excretion	• The primary route of ticagrelor elimination is hepatic metabolism. • The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. • The mean $t_{½}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

CYP = cytochrome P450; $t_{½}$ = terminal half-life; t_{max} = time to maximum plasma concentration.
Data from BRILINTA Prescribing Information 2011.

See page 19 for Full Prescribing Information

Clinical Studies

The clinical evidence for the effectiveness of BRILINTA™ was derived from the pivotal PLATelet inhibition and patient Outcomes (PLATO) trial, a randomized double-blind study that compared ticagrelor with clopidogrel, both given in combination with aspirin and other standard therapy, in patients with ACS (James 2009, Wallentin 2009, BRILINTA Prescribing Information 2011). A total of 18,624 patients participated in the study (9,333 in the ticagrelor group and 9,291 in the clopidogrel group). Patients hospitalized with documented evidence of ACS (UA, NSTEMI, or STEMI) within the previous 24 hours were eligible for inclusion. The two treatment groups were well balanced with regard to baseline characteristics (Table 2).

Ticagrelor was administered in a loading dose of 180 mg followed by a dosage of 90 mg twice daily. Patients in the clopidogrel group were given a 300-mg loading dose followed by a dosage of 75 mg daily if they had not received an open-label loading dose and had not used clopidogrel for 5 or more days before randomization. Concomitant aspirin was recommended at a loading dose of 160–500 mg. A daily maintenance dose of aspirin 75–100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment.

Treatment continued for a minimum of 6 months and a maximum of 12 months; the median period of drug expo-

PLATO Trial

- A randomized double-blind study comparing BRILINTA with clopidogrel, both given with aspirin and other standard therapy, in patients with ACS (UA, STEMI, NSTEMI) (N = 18,624)
- Patients could be included whether there was intent to manage the ACS medically or invasively
- Patients were allowed to receive a loading dose of clopidogrel prior to randomization
- Primary end point was the composite of first occurrence of cardiovascular (CV) death, nonfatal MI (excluding silent MI), or nonfatal stroke
- BRILINTA as compared with clopidogrel has been shown to decrease the rate of a combined end point of CV death, MI (excluding silent MI), or stroke
- The difference in treatments was driven by CV death and MI with no difference in stroke
- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75 mg to 100 mg per day.

TABLE 2
Baseline Characteristics of Patients in the PLATO Trial

Characteristic	Ticagrelor Group (n = 9,333)	Clopidogrel Group (n = 9,291)
Median age (y)	62.0	62.0
Age ≥ 75 y (%)	15.0	16.0
Sex (%)		
Male	71.6	71.7
Female	28.4	28.3
Median body weight (kg)	80.0	80.0
Median BMI[a]	27	27
Race (%)[b]		
White	91.8	91.6
Black	1.2	1.2
Asian	5.8	6.0
Other	1.2	1.2
Cardiovascular risk factors (%)		
Habitual smoker	36.0	35.7
Hypertension	65.8	65.1
Dyslipidemia	46.6	46.7
Diabetes mellitus	24.9	25.1
Other medical history (%)		
Myocardial infarction	20.4	20.7
PCI	13.6	13.1
CABG surgery	5.7	6.2
Congestive heart failure	5.5	5.8
Nonhemorrhagic stroke	3.8	4.0
Peripheral arterial disease	6.1	6.2
Chronic renal disease	4.1	4.4
History of dyspnea	15.1	14.6
COPD	5.9	5.7
Asthma	2.9	2.9
Gout	2.9	2.8
Troponin-I positive at entry (%)	85.3	86.1
Final diagnosis of ACS (%)		
NSTEMI	42.9	42.5
STEMI	37.5	38.0
Unstable angina	16.6	16.8
Other or missing data[c]	3.0	2.7

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; NSTEMI = non–ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

[a] BMI = Body Mass Index (weight in kilograms divided by square of height in meters [kg/m^2]).

[b] n = 9,332 for ticagrelor group.

[c] Includes patients with unspecified ACS or no ACS.

Source: Wallentin L, *et al. N Engl J Med* 2009;36:1045–1057. Copyright 2009 by the Massachusetts Medical Society. Reproduced with permission.

See page 19 for Full Prescribing Information

sure was 277 days.

The primary efficacy end point was the composite of cardiovascular death, nonfatal MI (excluding silent MI), or nonfatal stroke. The components of the primary end point were assessed as secondary end points.

The primary safety end point was the first occurrence of any PLATO-defined major bleeding event (fatal/life-threatening or other). PLATO used the following bleeding severity categorization:

• *Major bleed – fatal/life-threatening:* Any one of the following: fatal; intracranial bleed; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin of more than 5 g/dL; or transfusion of 4 or more units of whole blood or PRBCs for bleeding

• *Major bleed – other:* Any one of the following: significantly disabling (eg, intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in hemoglobin of 3 g/dL; or transfusion of 2 to 3 units of whole blood or PRBCs for bleeding.

• *Minor bleed:* Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).

• *Minimal bleed:* All others (eg, bruising, bleeding gums, oozing from injection site) not requiring intervention.

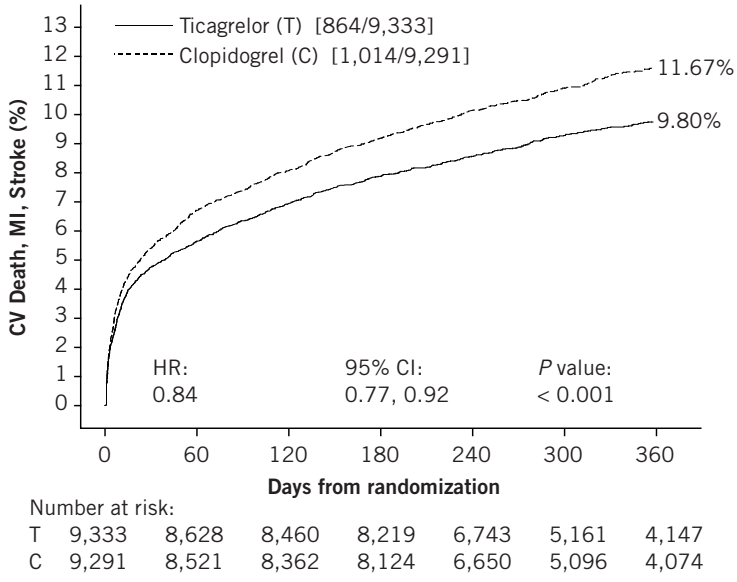
Safety end points also included minor bleeding, dyspnea, bradyarrhythmia, any other clinical adverse event, and results of laboratory safety tests.

TABLE 3
Patients With Outcome Events in PLATO (KM%)

	Ticagrelor + Aspirin (n = 9,333)	Clopidogrel + Aspirin (n = 9,291)	Hazard ratio (95% CI)	*P* Value
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Nonfatal MI	5.8	6.9	0.84	
Nonfatal stroke	1.4	1.1	1.24	
Secondary end points[a]				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI[b]	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke[b]	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

[a] First occurrence of specified event at any time.
[b] Includes patients that could have had other nonfatal events or died.

FIGURE 2
Time to First Occurrence of CV Death, MI, or Stroke in PLATO



HR = hazard ratio; CI = confidence interval.
Source: BRILINTA Prescribing Information 2011.

EFFICACY RESULTS

At 12 months, the primary efficacy end point (ie, a composite of cardiovascular death, nonfatal MI [excluding silent MI], or nonfatal stroke) occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs. 11.7%, respectively; $P < 0.001$) (Table 3).

The difference between treatments on the composite resulted from effects on cardiovasacular death and MI; each was statistically significant when considered as a secondary end point, and there was no beneficial effect on strokes. For all-cause mortality, the benefit was also statistically significant ($P = 0.0003$), with a hazard ratio of 0.78. However, because of the hierarchical test sequence used in PLATO, all-cause mortality was an exploratory analysis, and the *P* value was considered nominal.

The Kaplan-Meier curve in Figure 2 shows the time to first occurrence of the primary composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke in the overall study. The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12-month treatment period (RRR 16%).

See page 19 for Full Prescribing Information

REGIONAL DIFFERENCES

Results in the rest of the world compared with effects in North America (U.S. and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the U.S. subset. The statistical test for the U.S./non-U.S. comparison is statistically significant (P = 0.009), and the same trend is present for both cardiovascular death and nonfatal MI. The individual results and nominal P values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the cardiovascular mortality and nonfatal MI components, however, supports the possibility that the finding is reliable.

A wide variety of baseline and procedural differences between the U.S. and non-U.S. (including intended invasive vs. planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see whether they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

ASPIRIN DOSE

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator, and use patterns were very different in the U.S. and elsewhere, with about 8% of non-U.S. investigators using aspirin doses above 100 mg and 2% using aspirin doses above 300 mg, in contrast to U.S. practice, where 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA™ when used with low maintenance doses (less than 100 mg) of aspirin, and results analyzed by aspirin dose were similar in the U.S. and elsewhere.

Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary end point, cardiovascular death and nonfatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

PHARMACOGENETICS

In a genetic substudy of PLATO (N = 10,285), the effects of BRILINTA compared with clopidogrel on thrombotic events and bleeding were not significantly affected by CYP2C19 genotype.

Regional Differences and Aspirin Dose

- In the North American subgroup, BRILINTA was numerically inferior to clopidogrel. This effect was driven by the US subset
- While this could be due to chance, retrospective analyses support the possibility that this finding is reliable and due to aspirin maintenance dose
- Because these were unplanned subset analyses, these analyses must be treated with caution
- In PLATO, use of > 100 mg of aspirin decreased the effectiveness of BRILINTA
- Overall results favored BRILINTA when used with ≤ 100 mg of aspirin
- Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg
- Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA

See page 19 for Full Prescribing Information

Safety

WARNING: BLEEDING RISK

- BRILINTA™, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft (CABG) surgery. When possible, discontinue BRILINTA at least 5 days prior to any surgery
- Suspect bleeding in any patient who is hypo-tensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75 mg to 100 mg per day

Please read additional Important Safety Information on page 2.

CONTRAINDICATIONS

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population.

BRILINTA is contraindicated in patients with active pathological bleeding, such as peptic ulcer or ICH.

BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins.

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

Drugs that inhibit platelet function, including BRILINTA, increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (major plus minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non–CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased.

In general, risk factors for bleeding include older age, a history of bleeding disorders, the performance of percutaneous invasive procedures, and concomitant use of medications that increase the risk of bleeding, such as anticoagulant therapy, higher doses of aspirin, and chronic use of nonsteroidal anti-inflammatory drugs (NSAIDS).

When possible, BRILINTA should be discontinued 5 days prior to surgery. Clinicians should suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.

If possible, clinicians should manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events.

Concomitant Aspirin Maintenance Dose

In PLATO, the use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), clinicians should use BRILINTA with a maintenance dose of aspirin of 75 mg to 100 mg.

Moderate Hepatic Impairment

BRILINTA has not been studied in patients with moderate hepatic impairment. Clinicians should consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea

Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, clinicians should exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; BRILINTA may be continued without interruption.

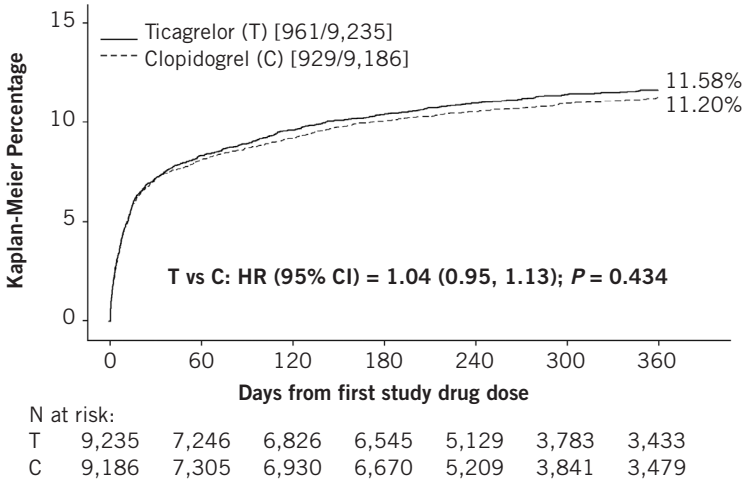
In a substudy, 199 patients from the PLATO trial underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after 1 month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA

Clinicians should avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (eg,

See page 19 for Full Prescribing Information

FIGURE 3
Kaplan-Meier Estimate of Time to First PLATO-Defined "Total Major" Bleeding Event



N at risk:

T	9,235	7,246	6,826	6,545	5,129	3,783	3,433
C	9,186	7,305	6,930	6,670	5,209	3,841	3,479

HR = hazard ratio; CI = confidence interval.
Source: BRILINTA Prescribing Information 2011.

to treat bleeding or for elective surgery), clinicians should restart it as soon as possible. Discontinuation of BRILINTA™ will increase the risk of MI, stent thrombosis, and death.

Strong Inhibitors of CYP3A

Ticagrelor is metabolized by CYP3A4/5. Clinicians should avoid the use of BRILINTA with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole.

Potent Inducers of CYP3A

Clinicians should avoid the use of BRILINTA with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Figure 3 shows major bleeding events over time in PLATO. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Annualized rates of bleeding are summarized in Table 4. About half of the bleeding events occurred during the first 30 days. As shown in Table 4, BRILINTA was associated with a somewhat greater risk of non–CABG-related bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared with clopidogrel.

In PLATO, 1,584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 5. Rates were very high but similar for BRILINTA and clopidogrel.

Although the platelet-inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, the PLATO trial did not show an advantage of BRILINTA compared with clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA-treated patients and in 79% of patients on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

DRUG DISCONTINUATION

In PLATO, the rates of study drug discontinuation attributed to adverse reactions were 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and in 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA™ patients and in 0.1% of clopidogrel patients.

COMMON ADVERSE EVENTS

A variety of nonhemorrhagic adverse events occurred in the PLATO trial at rates of 3% or more (Table 6). In the absence of a placebo control, whether these events are drug-related cannot be determined in most cases, except where they are more common with BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

BRADYCARDIA

In clinical studies, BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). The PLATO trial excluded patients at increased risk of bradycardic events

TABLE 4
Non–CABG-Related Bleeds (Kaplan-Meier %)

	Ticagrelor (n = 9,235)	Clopidogrel (n = 9,186)
Total (major + minor)	8.7	7.0
Major	4.5	3.8
Fatal/life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (fatal/life-threatening)	0.3	0.2

Source: BRILINTA Prescribing Information 2011.

See page 19 for Full Prescribing Information

TABLE 5
CABG Bleeds (Kaplan-Meier %)

Patients With CABG	Ticagrelor (n = 770)	Clopidogrel (n = 814)
Total major	85.8	86.9
Fata/life-threatening	48.1	47.9
Fatal	0.9	1.1

Source: BRILINTA Prescribing Information 2011.

(e.g., patients who had sick sinus syndrome, second- or third-degree atrioventricular block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope, and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of approximately 3,000 patients in the PLATO trial, more patients had ventricular pauses with BRILINTA™ (6.0%) than with clopidogrel (3.5%) in the acute phase; the rates were 2.2% and 1.6%, respectively, after 1 month.

GYNECOMASTIA

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and by 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex-organ malignancies, did not differ between the two treatment groups in the PLATO study.

TABLE 6
Percentage of Patients Reporting Nonhemorrhagic Adverse Events (at Least 3% or More in Either Group)

	Ticagrelor (n = 9,235)	Clopidogrel (n = 9,186)
Dyspnea[a]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Noncardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[a]Includes dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, and dyspnea paroxysmal nocturnal.
Source: BRILINTA Prescribing Information 2011.

LABORATORY ABNORMALITIES

Serum Uric Acid

Serum uric acid levels increased ap-proximately 0.6 mg/dL from baseline on BRILINTA and approxmately 0.2 mg/dL on clopidogrel in the PLATO trial. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

Serum Creatinine

In the PLATO study, a > 50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared with 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation wasobserved even in those with the greatest on-treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events, such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

DRUG INTERACTIONS

Effects of Other Drugs on BRILINTA

Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

CYP3A inhibitors. Clinicians should avoid the use of strong inhibitors of CYP3A (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin).

CYP3A inducers. Clinicians should avoid the use of BRILINTA™ with potent inducers of CYP3A (eg, rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital).

Aspirin. The use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA.

Effect of BRILINTA on Other Drugs

Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

Simvastatin and lovastatin. Treatment with BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Clinicians should avoid simvastatin and lovastatin doses greater than 40 mg.

Digoxin. Because of inhibition of the P-glycoprotein transporter, clinicians should monitor digoxin levels with initiation of or any change in BRILINTA therapy.

Other concomitant therapy. BRILINTA can be administered with unfractionated or low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, ACE inhibitors, and angiotensin receptor blockers.

63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had

See page 19 for Full Prescribing Information

USE IN SPECIFIC POPULATIONS

Pregnancy

BRILINTA is a Pregnancy Category C drug. There are no adequate and well-controlled studies of the use of BRILINTA™ in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses approximately 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at dosages from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60-kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of the pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at dosages from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dosage of delayed gall bladder development, and incomplete ossification of the hyoid, pubis, and sternebrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at dosages of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at a dosage of 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects, such as delays in pinna unfolding and eye opening, occurred at doses of 10 and 60 mg/kg (approximately one half and 3.2 times the MRHD on a mg/m^2 basis).

Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA™, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of BRILINTA in pediatric patients have not been established.

Geriatric Use

In the PLATO trial, 43% of patients were 65 years of age and older, and 15% were 75 years of age and older. The relative risk of bleeding was similar in both treatment and age groups.

No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

BRILINTA has not been studied in patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver, and impaired hepatic function can increase the risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment, and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment.

Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied.

See page 19 for Full Prescribing Information

Dosage and Administration

DOSAGE AND ADMINISTRATION

BRILINTA™ therapy should be initiated with a 180-mg (two 90-mg tablets) loading dose, and treatment should be continued with 90 mg twice daily.

After the initial loading dose of aspirin (usually 325 mg), BRILINTA should be used with a daily maintenance dose of aspirin of 75 mg to 100 mg.

Patients with ACS who have received a loading dose of clopidogrel may be started on BRILINTA.

BRILINTA can be administered with or without food.

A patient who misses a dose of BRILINTA should take one 90-mg tablet (their next dose) at its scheduled time.

HOW SUPPLIED

BRILINTA (ticagrelor) 90 mg is supplied as round, biconvex, yellow, film-coated tablets marked with a "90" above "T" on one side.

The following presentations of BRILINTA are available:

Bottles of 60	NDC 0186-0777-60
Bottles of 180	NDC 0186-0777-18
100-count Hospital Unit Dose	NDC 0186-0777-39

STORAGE AND HANDLING

BRILINTA should be stored at 25°C (77°F); excursions are permitted to 15°–30°C (59°–86°F).

Keep BRILINTA in the container it comes in.

Keep BRILINTA tablets dry.

See page 19 for Full Prescribing Information

P&T Committee Considerations

INTRODUCTION

ACS is a leading cause of morbidity and mortality in the United States. According to the Heart Disease and Stroke Statistics 2011 Update from the American Heart Association, 1,172,000 hospital discharges in the U.S. were due to ACS in 2007. Of these, 731,000 (62.4%) were for MI alone; 431,000 (36.8%) were for unstable angina alone; and 10,000 (0.9%) were for both diagnoses (Roger 2011).

BRILINTA CLINICAL EFFECTIVENESS

BRILINTA™ (ticagrelor) is the first reversibly binding oral $P2Y_{12}$ ADP receptor antagonist (James 2009). Ticagrelor is not a prodrug and does not require metabolic activation to inhibit the $P2Y_{12}$ receptor; however, it is converted in the liver into an active metabolite, which is approximately equipotent (James 2009).

BRILINTA is indicated to reduce the rate of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS)(unstable angina, non–ST-elevation myocardial infarction, or ST-elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined end point of CV death, myocardial infarction (MI), or stroke compared with clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, BRILINTA also reduces the rate of stent thrombosis (BRILINTA Prescribing Information 2011).

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin over 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin over 100 mg daily (BRILINTA Prescribing Information 2011).

The PLATO trial was a phase-3, randomized, double-blind, parallel-group, event-driven study that compared BRILINTA with clopidogrel in more than 18,000 hospitalized patients with ACS (James 2009, Wallentin 2009). In this pivotal study, treatment with BRILINTA, as compared with clopidogrel, significantly reduced the rate of first occurrence of the study's composite end point of cardiovascular death, nonfatal MI (excluding silent MI), or stroke. BRILINTA also reduced the secondary end points of cardiovascular death and MI individually, with no difference in stroke. BRILINTA and clopidogrel were studied with aspirin and other standard therapies.

BRILINTA was asociated with a somewhat higher rate of non–CABG-related major bleeding compared with clopidogrel (4.5% vs. 3.8%, respectively). In patients who underwent CABG surgery, the rates of total major bleeding were similar in the BRILINTA and clopidogrel groups (85.8% vs. 86.9%, respectively).

RISK EVALUATION AND MITIGATION STRATEGY

The Risk Evaluation and Mitigation Strategy (REMS) for BRILINTA has two goals: (1) to inform health care professionals and patients about the risks associated with BRILINTA, particularly the risk of bleeding, and (2) to inform health care professionals and patients that the maintenance dose of aspirin, coadministered with BRILINTA, should not exceed 100 mg (BRILINTA REMS Document 2011). Components of the BRILINTA REMS initiative include a Medication Guide, a Communication Plan, and the submission of REMS assessments to the FDA.

Medication Guide

A Medication Guide is dispensed with each BRILINTA prescription. The Guide is also available on the BRILINTA REMS Web site (www.brilintarems.com) or by calling 1-800-236-9933. The Medication Guide includes information to support patient counseling regarding the risks and benefits of treatment with BRILINTA.

The Medication Guide is not intended to replace discussions between patients and their health care providers regarding the patient's condition and its treatment. Rather, the Guide provides information about the use of BRILINTA to lower the risk of a heart attack or stroke. For instance, the Guide informs patients that BRILINTA (and similar drugs) can cause serious bleeding, such as internal bleeding, that can require blood transfusions or surgery, and that this bleeding can result in death. Patients are instructed to contact their physician immediately if they have signs or symptoms of bleeding while taking BRILINTA, such as bleeding that is severe or that cannot be controlled; pink, red, or brown urine; and red or black stools.

The Medication Guide warns patients not to discontinue BRILINTA without first talking to their physician. The Guide points out that if patients with a stent stop taking BRILINTA too soon, they are at increased risk of developing a blood clot in the stent, having a heart attack, or dying. Patients also are told not to stop taking BRILINTA because of bleeding or for other reasons because their risk of a heart attack or stroke may increase.

Patients are advised that BRILINTA is administered with aspirin and that they should not take a dosage of aspirin that is higher than 100 mg daily because it can affect how BRILINTA works.

Other topics covered by the Medication Guide include:

- A description of BRILINTA™
- Who should not take BRILINTA
- What patients should tell their physicians before

See page 19 for Full Prescribing Information

taking BRILINTA
- How BRILINTA should be taken
- The possible side effects of BRILINTA
- How BRILINTA should be stored

Communication Plan

A Communication Plan tailored for health care professionals who are likely to prescribe and dispense BRILINTA is the second component of the REMS program (BRILINTA REMS Document 2011). The primary objective of the Communication Plan is to inform health care professionals of the serious risks associated with BRILINTA, particularly the increased risk of bleeding, and to inform them that the daily maintenance dose of aspirin, co-administered with BRILINTA, should not exceed 100 mg (BRILINTA REMS Document 2011). The Communication Plan consists of three parts: (1) a "Dear Healthcare Professional" letter; (2) a BRILINTA REMS Web site; and (3) a "Professional Organization" letter.

The "Dear Health Care Professional" letter will be distributed electronically or by postal mail to interventional cardiologists, clinical cardiologists, emergency medicine physicians, internal medicine physicians, primary care physicians, nurse practitioners, physician assistants, pharmacists, critical care nurses, and cardiac nurse specialists. The letter was distributed within 60 days after the initial REMS approval date and will be distributed again at 6, 12, and 24 months after approval. Product labeling and the Medication Guide will be provided in conjunction with the letter.

The BRILINTA REMS Web site was launched within 30 days after REMS approval. The site will provide information for health care professionals and patients for 2 years after product launch. Visitors to the site will learn about the goals of the REMS program and about the risks of treatment with BRILINTA. In addition, they will have access to the product's package insert, the Medication Guide, and the "Dear Health Care Professional" letter.

A "Professional Organization" letter was distributed within 60 days of the REMS approval date. This letter contains the same information that is found in the "Dear Health Care Professional" letter. AstraZeneca will request that professional organizations disseminate this information to their members. Product labeling and the Medication Guide will be provided in conjunction with the letter.

Recipients of the "Professional Organization" letter will include the American Heart Association, the American College of Cardiologists, the Society for Cardiovascular Angiography and Interventions, the American College of Chest Physicians, the American Academy of Family Physicians, the American Society of Health-System Pharmacists, and other groups.

Submission of REMS Assessments to the FDA

The final component of the REMS program consists of the submission of REMS assessments to the FDA by AstraZeneca at 18 months, 3 years, and 7 years after approval of the REMS plan (BRILINTA REMS Document 2011). To facilitate the inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment.

See page 19 for Full Prescribing Information

Conclusion

In view of the overall health impact of ACS, as well as its significant economic burden, P&T decision makers need to identify optimal treatment approaches to this debilitating and potentially fatal disorder.

BRILINTA™ (ticagrelor) is the first cyclopentyltriazolopyridine in a new class of antiplatelets. BRILINTA interacts with the $P2Y_{12}$ ADP receptor, which is approved for the reduction of thrombotic cardiovascular events in patients with ACS. Ticagrelor is not a prodrug and does not require metabolic activation to inhibit the $P2Y_{12}$ receptor; however, hepatic metabolism is needed to produce its active metabolite.

In the pivotal phase-3 PLATO trial, BRILINTA significantly reduced the rate of first occurrence of the study's composite end point of cardiovascular death, nonfatal MI (excluding silent MI), or stroke versus clopidogrel. BRILINTA also reduced the secondary end points of cardiovascular death and MI individually, with no difference in stroke versus clopidogrel.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Maintenance doses of aspirin above 100 mg should be avoided.

Like other antiplatelet agents, BRILINTA can cause significant, sometimes fatal, bleeding. BRILINTA should not be used in patients with active pathological bleeding or a history of intracranial hemorrhage. BRILINTA should not be started in patients planned to undergo urgent CABG surgery.

When possible, discontinue BRILINTA at least 5 days prior to any surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures in the setting of BRILINTA. If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events.

BRILINTA is contraindicated in patients with a history of intracraial hemorrhage and active pathological bleeding, such as peptic ulcer. BRILINTA is also contraindicated in patients with severe hepatic impairment because of a probable increase in exposure. BRILINTA has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins.

The clinical use of BRILINTA is supported by a Risk Evaluation and Mitigation Strategy (REMS) initiative, which is designed to inform health care professionals and patients about the risks associated with BRILINTA, particularly the risk of bleeding, and about the need to ensure that the maintenance dose of aspirin, co-administered with BRILINTA, does not exceed 100 mg.

See page 19 for Full Prescribing Information

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GLOSSARY OF ABBREVIATIONS

ACS	acute coronary syndrome
ADP	adenosine diphosphatase
CABG	coronary artery bypass graft
CYP	cytochrome P450
FDA	Food and Drug Administration
IPA	inhibition of platelet aggregation
MI	myocardial infarction
MRHD	maximum recommended human dose
NSTEMI	non–ST-elevation myocardial infarction
PCI	percutaneous coronary intervention
PLATO	PLATelet inhibition and patient Outcomes
REMS	Risk Evaluation and Mitigation Strategy
STEMI	ST-elevation myocardial infarction

See page 19 for Full Prescribing Information

1015105

BRILINTA™
(ticagrelor)
Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRILINTA safely and effectively. See full prescribing information for BRILINTA.

BRILINTA™ (ticagrelor) tablets, for oral use

Initial U.S. Approval: 2011

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

INDICATIONS AND USAGE

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. (1)

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily. (1, 5.2, 14)

DOSAGE AND ADMINISTRATION

- Initiate treatment with 180 mg (two 90 mg tablets) oral loading dose. (2)
- Continue treatment with 90 mg twice daily. (2)
- After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2)

DOSAGE FORMS AND STRENGTHS

- 90 mg tablets (3)

CONTRAINDICATIONS

- History of intracranial hemorrhage (4.1)
- Active pathological bleeding (4.2)
- Severe hepatic impairment (4.3)

WARNINGS AND PRECAUTIONS

- Like other antiplatelet agents, BRILINTA increases the risk of bleeding. (5.1)
- In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. (5.2, 14)
- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. (5.3)
- Dyspnea: Dyspnea was reported more frequently with BRILINTA than with clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes. (5.4)
- Discontinuation of BRILINTA: Premature discontinuation increases the risk of myocardial infarction, stent thrombosis, and death. (5.5)

ADVERSE REACTIONS

Most common adverse reactions are bleeding 12% and dyspnea 14%. (5.1, 5.4, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Avoid use with strong CYP3A inhibitors or CYP3A inducers. (7.1, 7.2)
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.3)
- Monitor digoxin levels with initiation of or any change in BRILINTA. (7.4)

See 17 For PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

1 INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [see *Clinical Studies* (14)].

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [see *Warnings and Precautions* (5.2) and *Clinical Studies* (14)].

2 DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily.

After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg.

ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA.

BRILINTA can be administered with or without food.

A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

3 DOSAGE FORMS AND STRENGTHS

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

4 CONTRAINDICATIONS

4.1 History of Intracranial Hemorrhage

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [see *Clinical Studies* (14)].

4.2 Active Bleeding

BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [see *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.1)].

4.3 Severe Hepatic Impairment

BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [see *Clinical Pharmacology* (12.3)].

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [see *Adverse Reactions* (6.1)].

In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]).

When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see *Warnings and Precautions* (5.5) and *Adverse Reactions* (6.1)].

5.2 Concomitant Aspirin Maintenance Dose

In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [see *Dosage and Administration* (2) and *Clinical Studies* (14)].

5.3 Moderate Hepatic Impairment

BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

5.4 Dyspnea

Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption.

In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

5.5 Discontinuation of BRILINTA

Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

5.6 Strong Inhibitors of Cytochrome CYP3A

Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.3)].

5.7 Cytochrome CYP3A Potent Inducers

Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea [see *Warnings and Precautions* (5.4)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

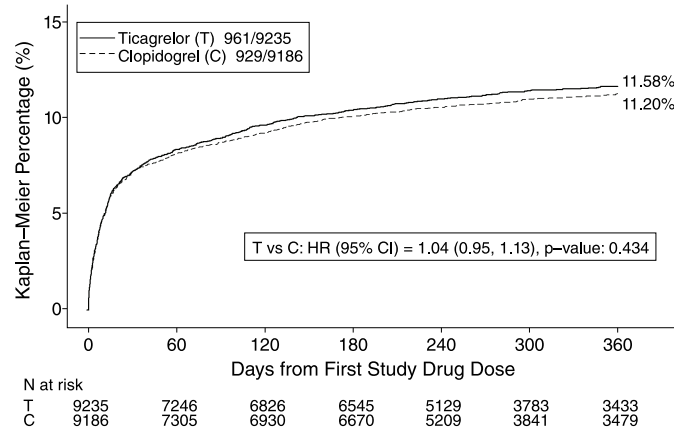
Bleeding

PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events

A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA N=9235	Clopidogrel N=9186
Dyspnea[a]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[a] Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia

In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities

Serum Uric Acid:

Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

Serum Creatinine:

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

7 DRUG INTERACTIONS

Effects of other drugs

Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

7.1 CYP3A inhibitors

Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) [see *Warnings and Precautions* (5.6) and *Clinical Pharmacology* (12.3)].

7.2 CYP3A inducers

Avoid use with potent inducers of CYP3A (e.g., rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital) [see *Warnings and Precautions* (5.7) and *Clinical Pharmacology* (12.3)].

7.3 Aspirin

Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [see *Warnings and Precautions* (5.2) and *Clinical Studies* (14)].

Effect of BRILINTA on other drugs

Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

7.4 Simvastatin, lovastatin

BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [see *Clinical Pharmacology* (12.3)].

7.5 Digoxin

Digoxin: Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy [see *Clinical Pharmacology* (12.3)].

7.6 Other Concomitant Therapy

BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

8.3 Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of BRILINTA in pediatric patients have not been established.

8.5 Geriatric Use

In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups.

No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment [see *Contraindications* (4), *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

8.7 Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied [see *Clinical Pharmacology* (12.3)].

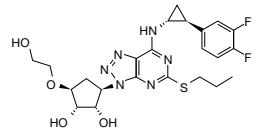
10 OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

11 DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. Chemically it is (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The chemical structure of ticagrelor is:



Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 µg/mL at room temperature.

BRILINTA tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

12.2 Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 µM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 2, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 µM ADP.

As shown in Figure 3, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in figure 3 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4% and from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interruption of antiplatelet effect [see *Dosage and Administration* (2)].

12.3 Pharmacokinetics

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

Absorption

Absorption of ticagrelor occurs with a median t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36%, (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC. BRILINTA can be taken with or without food.

Figure 2 Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor, or 600 mg clopidogrel

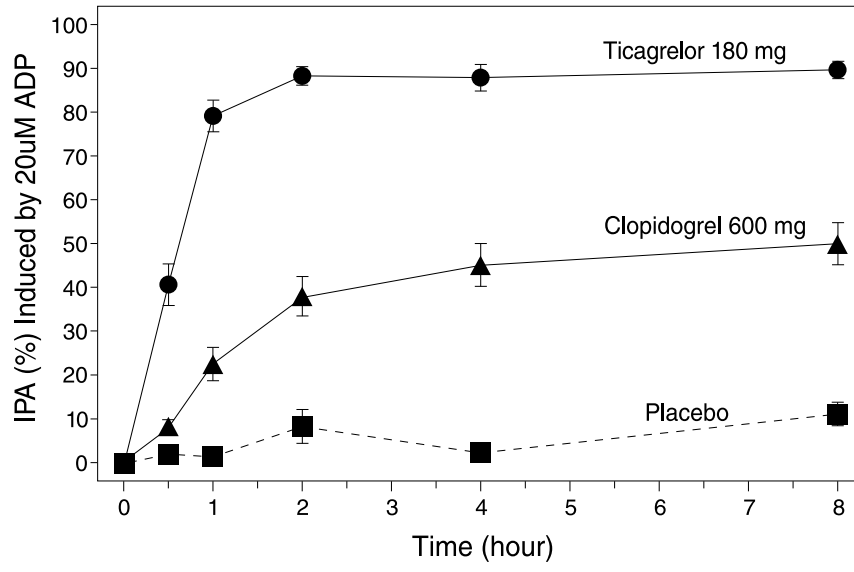
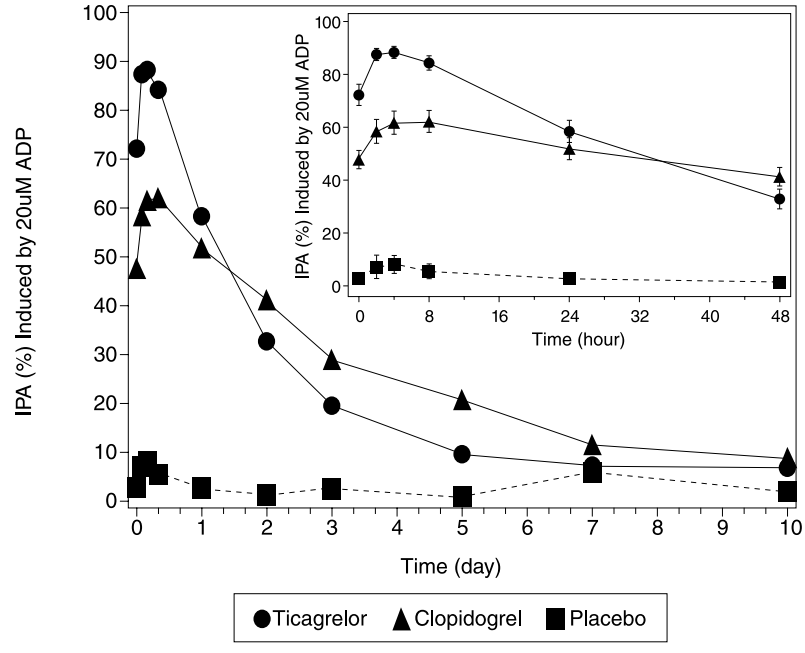


Figure 3 Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



Distribution

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

Metabolism

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

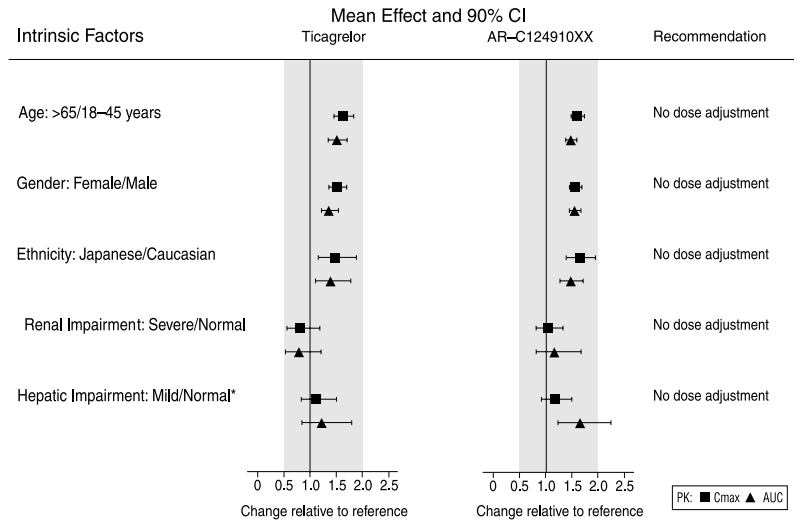
Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Special Populations

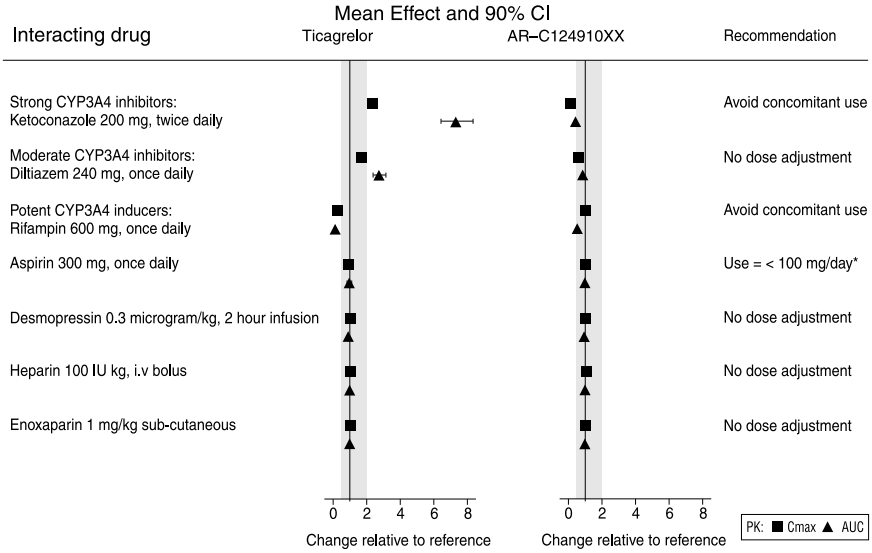
The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 4. Effects are modest and do not require dose adjustment.

Figure 4 Impact of intrinsic factors on the pharmacokinetics of ticagrelor



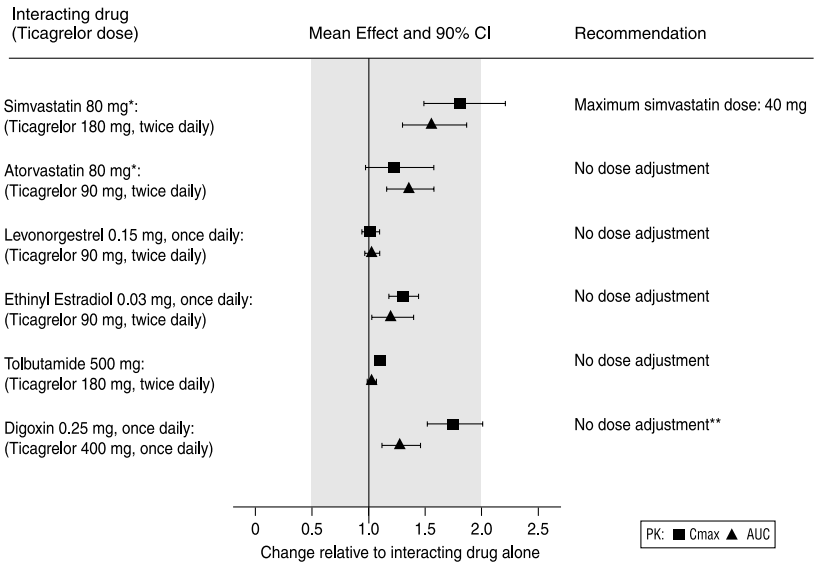
*BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

Figure 5 Effect of co-administered drugs on the pharmacokinetics of ticagrelor



*See *Dosage and Administration (2)*.

Figure 6 Impact of BRILINTA on the pharmacokinetics of co-administered drugs



*Similar increases in AUC and C_{max} were observed for all metabolites
**Monitor digoxin levels with initiation of or change in BRILINTA therapy

Pediatric
Ticagrelor has not been evaluated in a pediatric population [see *Use in Specific Populations* (8.4)].

Body Weight
No dose adjustment is necessary for ticagrelor based on weight.

Smoking
Habitual smoking increased population mean clearance of ticagrelor by approximately 22% when compared to non-smokers. No dose adjustment is necessary for ticagrelor based on smoking status.

Effects of Other Drugs on BRILINTA

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 5 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels.

Effects of BRILINTA on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific *in vivo* effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, and digoxin, see Figure 6.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of BRILINTA is derived from PLATO, a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS). Patients were treated for at least 6 months and for up to 12 months. Study endpoints were obtained until the study was complete, even if drug was discontinued.

Patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms were randomized to receive BRILINTA or clopidogrel. Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent. Subjects in the clopidogrel arm were

treated with an initial loading dose of clopidogrel 300 mg, if previous clopidogrel therapy had not been given prior to randomization. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. All subjects randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Concomitant aspirin was recommended at a loading dose of 160-500 mg. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment.

Because of ticagrelor's metabolism by CYP3A enzymes, the protocol recommended limiting the maximum dosage of simvastatin and lovastatin to 40 mg in both study arms. Because of an increased bleeding risk, the study excluded patients with previous intracranial hemorrhage, a gastrointestinal bleed within the past 6 months, or other factors that predispose to bleeding.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years.

The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke. The components were assessed as secondary endpoints.

Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 4 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

The difference between treatments on the composite resulted from effects on CV death and MI; each was statistically significant when considered as a secondary endpoint and there was no beneficial effect on strokes. For all-cause mortality the benefit was also statistically significant (p = 0.0003) with a hazard ratio of 0.78.

Among 11289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated "definite") than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; p=0.0091). The results were similar for drug-eluting and bare metal stents.

The Kaplan-Meier curve (Figure 7) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study.

The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12 month treatment period (RRR 16%).

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Many of these are shown in Figure 8. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two marked exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., final diagnosis, aspirin maintenance dose, use of PCI). Patients were not stratified by initial diagnosis, but the effect in the unstable angina subset (determined after randomization) appeared smaller than the effect in the NSTEMI and STEMI subsets. The results in the subsets based on final diagnosis (STEMI, NSTEMI and unstable angina) are also presented in Figure 8.

Regional Differences

Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison

Table 4 Patients with Outcome Events, in PLATO (KM%)

	BRILINTA N=9333	Clopidogrel N=9291	Hazard Ratio (95% CI)	p-value
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Non-fatal MI	5.8	6.9	0.84	
Non-fatal stroke	1.4	1.1	1.24	
Secondary endpoints[a]				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI[b]	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke[b]	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

a First occurrence of specified event at any time b Includes patients that could have had other non-fatal events or died

Figure 7 Time to First Occurrence of CV Death, MI, or Stroke in PLATO

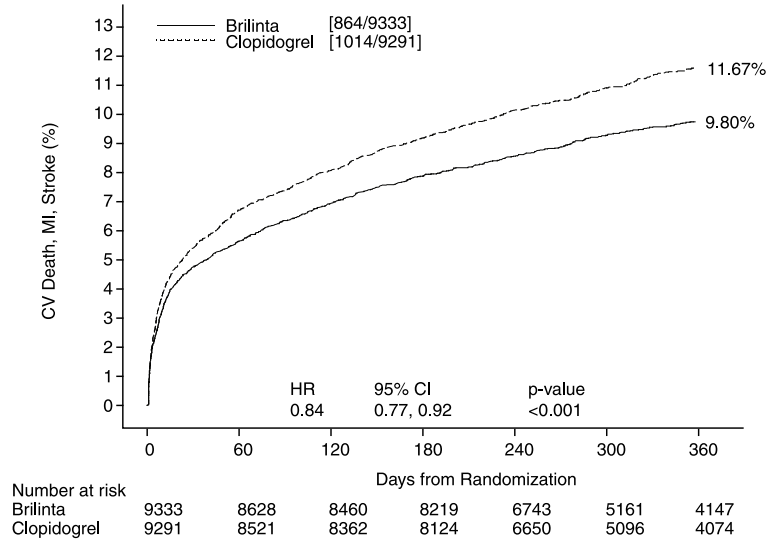


Figure 8 Subgroup analyses of PLATO

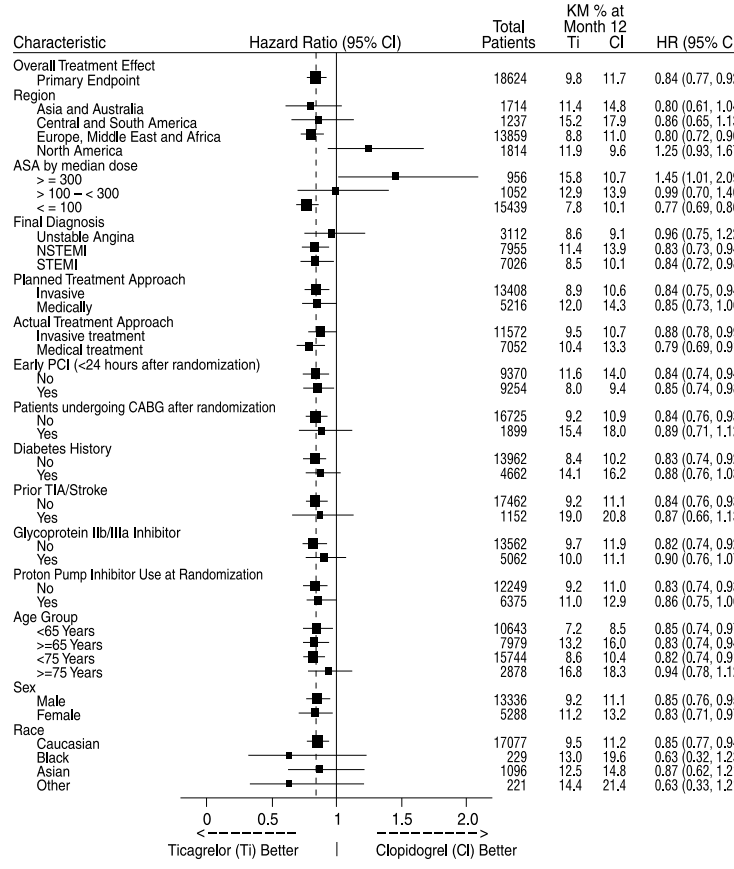
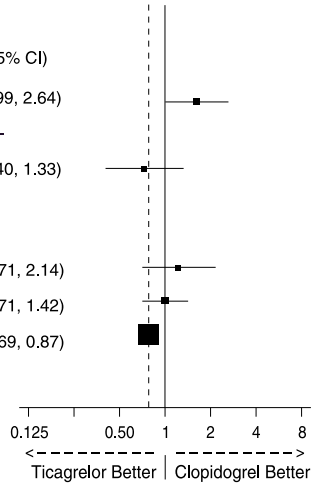


Table 5 PLATO: CV Death, MI, Stroke by maintenance aspirin dose in the US and outside the US

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor Events	Clopidogrel N	Clopidogrel Events	HR (95% CI)
US	>=300	324	40	352	27	1.62 (0.99, 2.64)
	>100 -<300	22	2	16	2	-
	<=100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	>=300	140	28	140	23	1.23 (0.71, 2.14)
	>100 -<300	503	62	511	63	1.00 (0.71, 1.42)
	<=100	7449	546	7443	699	0.78 (0.69, 0.87)



is statistically significant (p=0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable.

A wide variety of baseline and procedural differences between the US and non-US (including intended invasive vs. planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were very different in the US and elsewhere, with about 8% of non-US investigators using aspirin doses above 100 mg, and about 2% using doses above 300 mg, in contrast with US practice, where 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 8 shows overall results by median aspirin dose. Table 5 shows results by region and dose.

Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

Pharmacogenetics

In a genetic substudy of PLATO (n=10,285), the effects of BRILINTA compared to clopidogrel on thrombotic events and bleeding were not significantly affected by CYP2C19 genotype.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a “90” above “T” on one side.

Bottles of 60 – NDC 0186-0777-60
Bottles of 180 – NDC 0186-0777-18
100 count Hospital Unit Dose – NDC 0186-0777-39

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature].

Keep BRILINTA in the container it comes in.

Keep BRILINTA tablets dry.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Benefits and Risks

- Tell patients to take BRILINTA exactly as prescribed.
- Inform patients not to discontinue BRILINTA without discussing it with the prescribing physician.
- Tell patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.
- Tell patients to read the Medication Guide.

17.2 Bleeding

Inform patients that they:

- Will bleed and bruise more easily
- Will take longer than usual to stop bleeding
- Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that BRILINTA can cause shortness of breath. Tell them to contact their doctor if they experience unexpected shortness of breath, especially if severe.

17.4 Invasive Procedures

Instruct patients to:

- Inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure.
- Tell the doctor performing any surgery or dental procedure to talk to the prescribing physician before stopping BRILINTA.

17.5 Concomitant Medications

Tell patients to list all prescription medications, over-the-counter medications or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g. warfarin, heparin).

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Manufactured by:
AstraZeneca, AB S-151 85 Södertälje Sweden
Marketed by: AstraZeneca LP, Wilmington, DE 19850

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MEDICATION GUIDE

BRILINTA™ (brih-LIN-tah)

(ticagrelor)

Tablets

Read this Medication Guide before you start taking BRILINTA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about BRILINTA?

BRILINTA is used to lower your chance of having a heart attack or dying from a heart attack or stroke **but BRILINTA (and similar drugs) can cause bleeding that can be serious and sometimes lead to death.** In cases of serious bleeding, such as internal bleeding, the bleeding may result in the need for blood transfusions or surgery. While you take BRILINTA:

- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer than usual for any bleeding to stop

Call your doctor right away, if you have any of these signs or symptoms of bleeding while taking BRILINTA:

- bleeding that is severe or that you cannot control
- pink, red or brown urine
- vomiting blood or your vomit looks like "coffee grounds"
- red or black stools (looks like tar)
- coughing up blood or blood clots

Do not stop taking BRILINTA without talking to the doctor who prescribes it for you. People who are treated with a stent, and stop taking BRILINTA too soon, have a higher risk of getting a blood clot in the stent, having a heart attack, or dying. If you stop BRILINTA because of bleeding, or for other reasons, your risk of a heart attack or stroke may increase.

When instructed by your doctor, you should stop taking BRILINTA 5 days before you have elective surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

Taking BRILINTA with aspirin

BRILINTA is taken with aspirin. Talk to your doctor about the dose of aspirin that you should take with BRILINTA. You should not take a dose of aspirin higher than 100 mg daily because it can affect how well BRILINTA works. Do not take doses of aspirin higher than what your doctor tells you to take. Tell your doctor if you take other medicines that contain aspirin, and do not take new over-the-counter medicines with aspirin in them.

What is BRILINTA?

BRILINTA is a prescription medicine used to treat people who:

- have had a recent heart attack or severe chest pain that happened because their heart was not getting enough oxygen.
- have had a heart attack or chest pain and are being treated with medicines or with a procedure to open blocked arteries in the heart.

BRILINTA is used with aspirin to lower your chance of having another serious problem with your heart or blood vessels, such as heart attack, stroke, or blood clots in your stent. These can be fatal.

Platelets are blood cells that help with normal blood clotting. BRILINTA helps prevent platelets from sticking together and forming a clot that can block an artery.

It is not known if BRILINTA is safe and works in children.

Who should not take BRILINTA?

Do not take BRILINTA if you:

- are bleeding now
- have a history of bleeding in the brain
- have bleeding from your stomach or intestine now (an ulcer)
- have severe liver problems

When instructed by your doctor, you should stop taking BRILINTA 5 days before you have elective surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

What should I tell my doctor before taking BRILINTA?

Before you take BRILINTA, tell your doctor if you:

- have had bleeding problems in the past
- have had any recent serious injury or surgery
- plan to have surgery or a dental procedure
- have a history of stomach ulcers or colon polyps
- have lung problems, such as COPD or asthma
- have liver problems
- have a history of stroke
- are pregnant, or are plan to become pregnant. It is not known if BRILINTA will harm your unborn baby. You and your doctor should decide if you will take BRILINTA.
- are breastfeeding. It is not known if BRILINTA passes into your breast-milk. You and your doctor should decide if you will take BRILINTA or breastfeed. You should not do both without talking with your doctor.

Tell all of your doctors and dentists that you are taking BRILINTA. They should talk to the doctor who prescribed BRILINTA for you before you have any surgery or invasive procedure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. **BRILINTA may affect the way other** medicines work, and other medicines may affect how BRILINTA works.

Especially tell your doctor if you take:

- an HIV-AIDS medicine
- medicine for heart conditions or high blood pressure
- medicine for high blood cholesterol levels
- an anti-fungal medicine by mouth
- an anti-seizure medicine
- a blood thinner medicine
- rifampin (Rifater, Rifamate, Rimactane, Rifadin)

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take BRILINTA?

- Take BRILINTA exactly as prescribed by your doctor.
- Your doctor will tell you how many BRILINTA tablets to take and when to take them.
- Take BRILINTA with a low dose (not more than 100 mg daily) of aspirin. You may take BRILINTA with or without food.
- Take your doses of BRILINTA around the same time every day.
- If you forget to take your scheduled dose of BRILINTA, take your next dose at its scheduled time. Do not take two doses at the same time unless your doctor tells you to.
- If you take too much BRILINTA or overdose, call your doctor or poison control center right away, or go to the nearest emergency room.

What are the possible side effects of BRILINTA?

BRILINTA can cause serious side effects, including:

- **See "What is the most important information I should know about BRILINTA?"**
- **Shortness of breath.** Call your doctor if you have new or unexpected shortness of breath when you are at rest, at night, or when you are doing any activity. Your doctor can decide what treatment is needed.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of BRILINTA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BRILINTA?

- Store BRILINTA at room temperature between 59°F to 86°F (15°C to 30°C).

Keep BRILINTA and all medicines out of the reach of children.

General information about BRILINTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BRILINTA for a condition for which it was not prescribed. Do not give BRILINTA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about BRILINTA. If you would like more information about BRILINTA, talk with your doctor. You can ask your pharmacist or doctor for information about BRILINTA that is written for health professionals.

For more information call 1-800-236-9933 or go to www.Brilinta.com.

What are the ingredients in BRILINTA?

Active ingredient: ticagrelor

Inactive ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

Issued: 07/2011

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Marketed by: AstraZeneca LP, Wilmington, DE 19850

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